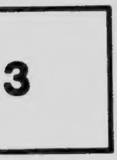
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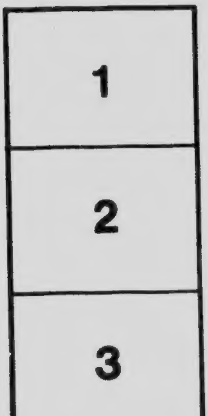
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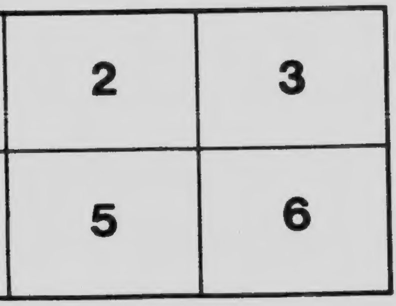
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PHYSIOLOGICAL SERIES

No. 29: SOME RECENT WORK ON THE CONTROL OF THE RESPIRATORY CENTRE, BY J. J. R. MACLEOD

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SOME RECENT WORK ON THE CONTROL OF THE RESPIRATORY CENTER

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Some Recent Work on the Control of the Respiratory Center

FROM the moment the animal is born until death, breathing proceeds with a rhythm which is occasionally broken for brief periods of time by voluntary holding of the breath or by participation of the respiratory musculature in the various expulsive acts of the body, or in phonation and singing. The respiratory movements involve the harmonious activities of greatly diverse muscular groups, some of them contracting, while others relax, but always in so perfect a synchronism that the movement produced alters the capacity of the thorax in the manner which will most effectively ventilate the pulmonary alveoli. During inspiration, for example, the muscles which elevate the thoracic cage and those which depress the diaphragm contract at the same time that the muscles of the abdominal walls relax to make more room for the depressed viscera.

The excitatory or inhibitory nerve impulses which control these movements come finally, of course, from the cells of the lower neurones and these are scattered along the cerebrospinal axis from the level of the nerve centers for the muscles of the alæ nasi in the pons to those of the abdominal muscles in the lumbar region of the spinal cord. But it is plain that these centers can not in themselves be more than local executives for a higher command which must have its headquarters in some more or less localized group of nerve cells. This chief respiratory center, as it is called, is usually considered to be situated in the medulla oblongata but there is good reason for believing that its upper limits extend for some distance into and perhaps beyond the pons.

It is clear that the fundamental problems of respiratory control must be directed to ascertain the conditions which excite or alter the activity of this center, and it is around this question that much important work has been contributed during recent years, particularly by the Oxford School of Physiologists led by J. S. Haldane[1] and the Copenhagen School led by August Krogh.

There are in general two ways in which the activities of a center might be caused to alter. These are by changes in the chemical composition of the blood supplying it and by nerve impulses derived from other parts of the nervous system.

Confining our attention for the present to the former class of influences, it may be said that tendency is to consider the hydrogen-ion concentration (C_H) of the blood that bathes the center as chiefly responsible. According to this view alterations in C_H furnish the respiratory hormone.

While there can be no doubt that the respiratory center is extremely sensitive to the slightest changes in C_H of the blood, indeed, it is probably safe to say that there is no more sensitive indicator of changes in C_H than the respiratory center, yet many serious objections can be raised against the view that the ordinary physiologic alterations in respiratory activity are brought about in this way. Because of the fact that the center is sensitive to changes in C_H which cannot be measured by any known laboratory method it is impossible to furnish direct proof for or against the hypothesis. All the evidence is of an indirect

nature and in many cases it is dependent upon assumptions and analogies which may possibly be erroneous.

It has long been known that respiratory activity can be excited by experimentally raising C_H of the blood, through the injection of mineral acids intravenously, but this does not necessarily mean that ordinary (physiologic) alterations in that function are due to the same cause. A great part of the indirect evidence is based on the observation that the tension of carbon dioxide (CO_2) in the blood bears a relationship to C_H of this fluid and to the degree of pulmonary ventilation. This is the case because CO_2 in solution is a weak acid and therefore cooperates with the other acids of blood to maintain C_H. It possesses one advantage over the other acids in that it is volatile and consequently can readily be got rid of through the alveoli. Whenever, therefore, there tends to be an increase in C_H of the blood some of the CO_2 which is in simple solution in the plasma is got rid of so that the tension declines and the percentage of CO_2 in the alveolar air becomes lower. The tension of CO_2, in other words, declines so as to make room in the blood for other acids. When the adjustment is perfect, the condition is often called *compensated acidosis*, but when there is too much fixed acid, so that C_H is slightly raised, it is called *uncompensated acidosis*. In the former case there is no respiratory disturbance when the person is at rest, but such is readily induced by the slightest exertion because there is a deficiency of basic substance available in the blood and tissues to combine with the increased CO_2, and other acids, produced by the active muscles; the *buffer action* of the blood is said to be depressed. In the latter case, on the other hand, there is hyperpnea even at rest.

The H-ion concentration may obviously be raised by a process which is fundamentally the reverse of that just considered; namely, by an increase in the CO_2 tension while the other (fixed) acids of the blood remain constant. In this case acidosis will occur and there will be hyperpnea along with a higher percentage of CO_2 in the alveolar air; this condition is styled carbonic acid[2] and it occurs in uncompensated cardiac cases and to a certain extent in asphyxial conditions and during strenuous muscular exertion.

In all of the foregoing instances the interpretation of the respiratory excitement which has almost universally been adopted is that C_H of the blood has become raised, but if we pause to consider all the facts, it will be seen that the conclusion is by no means inevitable. It may as well be that it is the free CO_2 as such, or more precisely the anion HCO'_3 (for $H_2CO'_3$ will dissociate into $H^{\cdot} \rightarrow HCO'_3$) that is the really important hormone instead of the cation $H^{\cdot}$. In the cases of carbonic acid acidosis this is easy to understand; in cases of uncompensated acidosis it may be explained if we remember that there is now no sufficient amount of base to take up and fix as carbonates the CO_2 as it is produced, so that the free CO_2 in the cells of the respiratory center, as in other cells, is not adequately removed. There is a certain amount of experimental support for this view of which the following may be cited: Hooker, Wilson and Connett succeeded in retarding death in the basal regions of the brain sufficiently so that respiratory movements were still present and they found that these movements became more markedly excited at a certain C_H of the perfusion fluid when the acid present was mainly H_2CO_3 than when it was any other acid. R. W. Scott

found that the respiratory movements in decerebrate cats were increased in proportion as the percentage of CO_2 in the respired air was raised. Examination of the arterial blood by the colorimetric method showed that C_H also became increased under these conditions, an observation which in itself, might support the view that it is really elevation of C_H that furnishes the stimulus to the respiratory center. That this is not the sole, if even the main, stimulus was shown in further experiments in which amounts of alkali were first of all injected intravenously so that decided depression in C_H of the blood was established. On now causing these "alkalosis" animals to respire in CO_2-rich atmospheres it was found that the respirations were excited practically to as great a degree as in the animals with normal C_H; although this became raised, it had not nearly attained the level at which it stands in normal blood even when very marked hyperpnea was present. Increase in CO_2 tension, quite independently of increase in C_H above the physiologic level, had quite clearly afforded the stimulus to the center. It will be necessary to repeat the observations by the use of the electrometric method for measuring C_H of the blood.

If further investigation should confirm the hypothesis that CO_2 tension is a more effective stimulus for the respiratory center than C_H it will mean that, unlike the rhythmic action of the heart which is highly susceptible to cations the rhythmic action of the respiratory center is so to anions. The excitability of the respiration center towards certain concentrations of the CN-ion is of great interest and significance in this connection although the action is differently explained by its discoverer, Loevenhart. The rhythmic contractions of the isolated small intestine are also highly susceptible to the influence of anions.

Apart from their theoretical interest the foregoing facts are of undoubted practical importance since they show that a certain tension of CO_2 must exist in the blood which bathes the respiratory, and very likely other centers, in order that the physiologic activity may be maintained. The observations recall the old hypothesis of Mosso that certain perversions of physiologic function may occur when the tension of CO_2 is subnormal (acapnia).

One of the most important questions in connection with the hormone control of the respiratory center concerns the influence of a deficiency of oxygen in the inspired air. It has long been known that dyspnea usually supervenes in atmospheres which are decidedly deficient in this gas. There are two well-known types of observation which illustrate this fact. The first of these is the laboratory experiment in which a person is caused to breathe in and out of a large spirometer or rubber bag provided with soda lime to absorb carbon dioxide, dyspnea develops, becoming very marked when the oxygen has fallen below 14 per cent. The other is afforded by watching the respiration at high altitudes, it is hyperpnea so that the alveoli are more thoroughly ventilated and the supply of oxygen in them becomes more frequently replenished in order to compensate for the decreased percentage in the atmosphere. There is therefore no doubt that deficiency of oxygen excites the respiration; the question is whether the stimulus is the oxygen deficiency *per se* or whether it is dependent upon some condition which is set up by this deficiency. In considering this question it is important to distinguish between extreme and moderate degrees of oxygen deficiency.

When it is extreme the respiratory center, like all other centers, becomes depressed apparently without any preliminary stimulation, and breathing ceases. Such a condition occurs when the blood supply to the medulla is seriously interfered with and in cases of respiration in poisonous gases, like carbon monoxide or methane. A similar depression of the respiratory center due to oxygen deficiency may possibly be the cause of death in such diseases as acute pneumonia and edema of the lungs. It is of decided practical value to know that it is possible to restore a center rendered inactive through deficiency of oxygen by increasing the percentage of this gas in simple solution in the blood supplying the medulla. We have observed this restorative power of oxygen inhalations very strikingly in the case of decerebrate cats (Fraser, Lang and Macleod). These animals breathe with perfect regularity as long as there is an adequate supply of oxygen to the medulla, but if this be curtailed, as by temporarily clamping the vertebral arterioles, the respirations gradually cease but return immediately the circulation is restored. Sometimes, especially when the arterio corpora quadrigemina are destroyed, the breathing in the decerebrate animals becomes irregular and gradually ceases entirely, though the heart is still beating and there is a fair arterial blood pressure. In such cases normal respiration is promptly restored by raising the partial pressure of oxygen in the alveolar air which is most conveniently done by introducing pure oxygen low down in the trachea through a catheter and interrupting the stream rhythmically at about the same rate as the animal breathes. The restored breathing continues for some time after discontinuing the oxygen inhalations.

In view of the results it is possible to explain the beneficial effects which often follow the administration of oxygen in cases of pneumonia, in coal gas poisoning, etc. The inhaled oxygen raises the tension of this gas in the alveolar air so that a sufficient amount of it becomes dissolved in the plasma to keep the center alive, independently—in the case of CO-poisoning at least—of the formation of more oxyhemoglobin. That nerve centers and other tissues can be kept alive by physiologic saline in which excess of oxygen is dissolved is a well-established fact and it should be our aim, when treating cases of asphyxia, to raise the partial pressure of this gas in the alveolar air as high as possible. The dissolved oxygen supplied to the centers in this way must be maintained until the mechanism of which the supply is normally ensured, namely, by dissociation of the oxygen bound to hemoglobin, has been restored to normal. The resuscitation afforded by increasing the percentage of oxygen in the alveolar air, although it can only be temporary, may serve to tide over a crisis and so permit the normal mechanisms by which oxygen is transported to the tissues to become restored.

With regard to the second method of respiratory control, namely, that through afferent nerve impulses only a few of the most outstanding facts can be referred to here. The older work seemed to show the most important of these impulses to be transmitted to the center along the vagus nerves and the hypothesis was formulated that the rate of the respiratory movements depends fundamentally on the fact that towards the end of each inspiration an impulse set up by the distention of the alveoli, is transmitted to the center where it inhibits the rhythmic discharge and so brings on an expiration. Without these inspiration

inhibitory impulses respiration is much slower and deeper than normal. There is a growing mass of evidence which goes to show that these afferent impulses, as well as others derived from the afferent nerves of the thoracic parietes (including muscular sense impressions) are important in harmonizing the action of the respiratory musculature much in the same way that afferent impulses from the extremities are important in the synthesis of the complicated muscular activities necessary for the maintenance of the erect posture and for locomotion (Pike,[5] Boothby and Berry[6]).

That the respiratory center is influenced by afferent impulses which are set up by the degree of distention of the lungs has been shown in experiments by Lois Fraser, Lang and Macleod.[7] The experiments were performed on decerebrate cats. When these animals were caused to breathe into wide-bore tubing provided with bottles containing soda lime to absorb the carbon dioxide it was found that the respiratory volume became markedly increased while there was still practically no reduction in the percentage of oxygen in the inspired air. This evidence, furnished by registration of the volume of respired air (by a Gad Krogh spirometer) was confirmed by observing the behavior of the respiratory quotient of the alveolar air. Immediately the breathing into the tubing was started the quotient rose considerably, sometimes to 2.0, indicating that CO_2 was being washed out of the blood by the more thorough ventilation of the alveoli. When the animal was allowed to breathe in outside air again the breathing respiratory volume quickly returned to the normal and the respiratory quotient fell to a very low level showing that the blood was now taking up the CO_2 it had lost.

This experiment recalls the experience of every one who has tried to breathe through tubing into a spirometer or gas absorbing apparatus; a certain degree of hyperpnea is always set up which is usually attributed to a conscious sense of effort. But the foregoing observations show clearly that the reaction is independent of the higher centers and that it must be purely reflex through the respiratory center, the afferent stimulus being the state of distention of the lungs or thorax. The stimulus which excites the hyperpnea may persist indefinitely or it may subside after a time. In cases in which it does not subside it will lead to an overventilation of the alveoli and consequently to a depletion of the free CO_2 of the blood (acapnia). It is possible that it is because of this condition that prolonged respiration through a gas mask or into a respiratory apparatus frequently becomes unbearable on account of the sense of bodily discomfort which develops (mask staleness).

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—*J. J. R. M.*

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